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ACCOMMODATING PHARMACOGENOMICS: FULFILLING
THE PROMISE OF INDIVIDUALIZED MEDICINE

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ABSTRACT

Pharmacogenomic technologies promise to usher in an era of individualized medicine, but also pose challenges to a regulatory regime without experience dealing with the sorts of data produced by these techniques. Pharmacogenomics as a field encompasses both “pharmacogenetic” techniques, which tend to focus on polymorphisms in cytochromes and other proteins involved in drug metabolism, and “pharmacogenomic” techniques such as microarray technologies, which examine disease and drug interactions on the level of the entire genome. In 2003, the FDA produced a guidance recommending procedures for the submission of pharmacogenomic data at the IND or NDA stage. While pharmacogenomic information used in “decision making” during trials is required, most pharmacogenomic data of an exploratory nature may be submitted voluntarily under a separate protocol. Though these procedures seem a reasonable means by which the FDA can open a dialogue with pharmaceutical manufacturers regarding the use of pharmacogenomic data, more action is necessary to develop the infrastructure necessary to develop the technology such that it may be incorporated in regulatory decisions with confidence.

I. INTRODUCTION

Ultimately, the medical profession treats patients, not conditions. Factors such as a patient's pattern of diet and exercise, occupational hazards, stresses, and personal medical histories will affect the course of treatment significantly. Diagnosis of a disease state is only one step among many necessary to develop an effective treatment regime. Ideally, many factors that might vary from patient to patient would be taken into account by a treating physician. Though fulfillment of the promise of "individualized medicine" is still some years away, much of the technology that could tailor treatment regimes to individual patients' genetic compositions – referred to as "pharmacogenomics" – is here. Given its integral role in influencing drug development strategies, the Food and Drug Administration (FDA) must begin to structure its requirements for submission of clinical data to accommodate pharmacogenomics, and must do so in the manner that best complements the development of the underlying technology.

When the FDA confirms the safety and efficacy of a medication, it approves the fitness of the drug for the treatment of a specific indication. In fact, many drugs are approved with as little as 30% efficacy among the general patient population.¹ The degree of specificity of this indication will vary, however. In a clinical setting, a medication is indicated for a condition if the detectable symptoms place the condition among the constellation of disorders that the medication has treated effectively in trials. If there is not some reliable measurable or observable characteristic that will differentiate the condition of one patient from that of another in a way that would predict a different response to the drug, the medication is approved for both patients. Some drugs will be ruled out for a given patient because they interact adversely with other drugs or cannot be used given certain metabolic disorders. For the most part, however, the variance in patient response is neither understood nor accounted for during the approval process.

Of course, there are very good reasons why the FDA cannot guarantee safety and efficacy for every patient taking a given medication and must often rely on trials that are not stratified on the basis of expected

¹See Allen D. Roses, *Pharmacogenetics and Drug Development: The Path to Safer and More Effective Drugs*, 5 NATURE REVIEWS: GENETICS 645, 648 (2004)

response. Putting aside the more familiar limits to assurance of safety and efficacy – degrees of patient compliance or differences in diet, for example, or the ethical paradox involving informed consent for trials involving children – some divergent patient responses are simply beyond the capacity of current medical technology to predict. Some variations could be due to differences in the underlying condition that are not readily diagnosed in a clinical setting, such as the precise identity of a pathogen or type of tumor. Other variations in patient response might be due to genetic differences that could account for variations in the bioavailability or metabolism of different medications, in the immune responses of patients, or in the etiologies of tumors.

Pharmacogenomics and pharmacogenetics promise to improve patient care by providing insight into the genetic components underlying the distribution of patient responses to disease and to treatment. Although these technologies are progressing rapidly, they are still in their nascent stages of development, and their utility in a clinical setting has not been established. As they have begun to mature and certain genotypes have been validated as predictive of clinical outcomes, questions have emerged regarding the FDA’s requirements for submission of pharmacogenomic data along with INDs, NDAs, or BLAs. The FDA sought to address these issues through a workshop involving industry representatives and FDA officials,² and these meetings eventually resulted in the publication of a draft guidance³ outlining FDA policy.

Because Congress has charged the FDA with safeguarding the supply of pharmaceuticals and biologics in the marketplace, FDA policy inevitably will play a major role in shepherding these promising technologies to maturity and into widespread clinical use. As FDA formulates policy, administrators must keep in mind

²Lawrence J. Lesko, et al., *Pharmacogenomics and Pharmacogenomics in Drug Development and Regulatory Decision Making: Report of the First FDA-PWG-PhRMA-DruSafe Workshop*, 43 J. CLINICAL PHARMACOLOGY 342 (2003)

³U.S. DEP’T OF HEALTH & HUMAN SERVICES, FOOD & DRUG ADMIN., CENTER FOR DRUG EVALUATION & RESEARCH (CDER), CENTER FOR BIOLOGICS EVALUATION & RESEARCH (CBER), CENTER FOR DEVICES & RADIOLOGICAL HEALTH (CDRH), GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS (November, 2003) (*hereinafter* “Guidance”)

a set of challenges that pharmacogenomics presents – challenges that are ethical, economic, and scientific in nature. This paper is designed to survey some of the emerging technologies and discuss some of the concerns the FDA has considered regarding their use in drug development.

II. PHARMACOGENETICS AND PHARMACOGENOMICS

While the terms are often used interchangeably, it may be useful to draw a functional distinction between pharmacogenetics and pharmacogenomics. The distinction is somewhat historical, as the term “pharmacogenetics” was first used to describe the study of genetic variation in genes such as the CYP450 family (discussed below,) involved in primary drug metabolism.⁴ The term “pharmacogenomics” refers to a more recent approach to the study of genetic and pharmacologic interaction on the level of the whole genome, wherein multiple genes or gene products are monitored in parallel and their interactions observed.. Because variations in proteins with a variety of functions, such as transporters and receptors, will affect metabolism, “pharmacogenomics” may be used both to distinguish studies broader than those focused on well-characterized metabolic enzymes, and to reflect the highly cooperative, complex processes underlying the efficacy, toxicity and metabolism of drugs.⁵

A. Pharmacogenetics

It has long been known that propensities toward certain illnesses have a genetic component. Even forty years ago, researchers were able to attribute differences in the metabolism of certain chemicals to variation in individual genes. In the 1960s, researchers recognized that inherited variation in the genes encoding the

⁴B.P. Sweeney, *Microarrays: New Pharmacogenomic Tools for the Twenty-First Century*, 21 EURO. J. OF ANAESTHESIOLOGY 505 (2004)

⁵*Id.*

enzymes butyryl-cholinesterase and N-acetyltransferase correlated with differences in the plasma or urine concentrations of different drugs.⁶ In the late 1980s, studies found a correlation between differences in metabolism of certain drugs and polymorphisms⁷ in a set of liver enzymes called cytochromes. Researchers found that several different variations in the sequence of the gene encoding cytochrome P-450 2D6 (CYP2D6), a protein involved in the metabolism of many drugs, correlated with rates of drug metabolism both more rapid and slower than typically seen in the population.⁸

Cytochrome P450 molecules are membrane enzymes containing iron that oxidize a wide variety of substrates – a surprisingly chemically diverse set of therapeutic molecules are metabolized by the same enzymes.^{7,8} The addition of an oxygen atom to a substrate will tend to improve the solubility of the molecule, generally an early step in the metabolism of lipid-based molecules.⁹ In the late 1970s, researchers found a correlation between polymorphisms in the gene encoding cytochrome CYP2D6 and the metabolism of the drug debrisoquine, used to treat hypertension.¹⁰ The CYP2D6 gene was later isolated, and it was found that a number of CYP2D6 polymorphisms persist in the general population. Comparing these polymorphisms with metabolic rate revealed a striking correlation. It was found that individuals with multiple copies of the gene metabolized many drugs more rapidly than those with a single copy. Individuals with mutations resulting in splicing errors or changes to amino acid sequence often had higher blood plasma concentrations of the drug, indicating slower metabolism. To date, 75 different alleles have been found, many of which are single nucleotide variations.¹¹ Despite this diversity, individuals are divided into four classes based on

⁶Richard Weinshilboum, *Inheritance and Drug Response*, 348 NEW ENGLAND J. OF MED. 529 (2003).

⁷A genetic polymorphism is defined to occur when two or more different single gene variants persist in more than 2% of a population. See Skada, R,..., Meyer, U, *Two Mutant Alleles of the Human Cytochrome P-450db1 (P450C2D1) Gene Associated with Deficient Metabolism of Debrisoquine And Other Drugs*. 85 PROC. NAT'L. ACAD. SCI. 5240 (1988).

⁸See Weinshilboum, *supra* note 6, at 530.

⁹See <http://www.its.caltech.edu/~atobias/RUP-p450.html>, last visited 3/16/05 (for a very humorous and only mildly objectionable website posted by an apparently very enthusiastic researcher, that, perhaps despite itself, gives a nice introduction to CYP450 basics for the layperson.)

¹⁰See Weinshilboum, *supra* note 6 at 530

¹¹See *id.* at 532

their CYP2D6 activity: patients with “ultrarapid metabolism” have multiple copies of the CYP2D6 gene, patients with “extensive metabolism” have a single working copy, and patients with slower enzymatic rates are characterized as having either “intermediate” or “poor metabolism.”¹² While nearly 75% of individuals exhibit “extensive metabolism,” the other classes are populated significantly. The frequency of alleles differs if patients are grouped by ethnicity. For example, 5 to 10% of whites and 1% of persons of Chinese or Japanese descent exhibit poor metabolism.¹³

Of the cytochromes, CYP2C9, CYP2C19, and CYP2D6 account for 40% of total cytochrome activity and show the most pronounced correlation between polymorphism and total metabolic rate.¹⁴ As a finite set of enzymes involved in the metabolism of numerous drugs, they represent promising candidates for genotyping in a clinical setting. If successful, clinical genotyping could become a routine procedure of use in the dosing of drugs, improving both safety and efficacy.

A number of diagnostic test kits have already been developed for use in a clinical laboratory setting. The pharmaceutical company Roche received FDA approval for the “AmpliChip CYP450” test system in January of 2005.¹⁵ The AmpliChip uses technology developed by the Affymetrix corporation in the context of genomic research and, according to Roche, will test for 29 different polymorphisms of CYP2D6 (including gene duplication and deletion) and two major polymorphisms in CYP2C19.¹⁶ Essentially, the “AmpliChip” device contains over 15,000 25 nucleotide strands (“oligonucleotides”) arrayed regularly on a glass chip the

¹²See Yosef Caraco, *Genes and the Response to Drugs*, 351 NEW ENGLAND J. OF MED. 2867 (2004)

¹³See *id.* at 2868

¹⁴See *id.* at 2868.

¹⁵See ROCHE, INC., ROCHE’S AMPLICHIP CYP450 TEST RECEIVES FDA CLEARANCE. Press Release (January, 2005)

¹⁶See *id.*

size of a dime. By amplifying and fluorescently labeling certain segments of DNA gained from a subject's blood sample, then allowing the products to form specific hydrogen bonds with the oligonucleotides fixed to the chip (the same specific interactions that hold together the two complementary strands of a DNA molecule,) a technician can determine a patient's genotype.

The AmpliChip is a diagnostic test that could be used to determine the dosing of a host of drugs the metabolism of which correlates with the function of CYP2D6 and CYP2C19. Until such testing is so cost effective as to be routine, however, it is likely that drugs developed and co-marketed with specific genetic tests will be more common. The first treatment co-marketed with a diagnostic test was the breast cancer drug trastuzumab, marketed by Genentech as Herceptin.¹⁷

Herceptin is a monoclonal antibody, rather than a small molecule drug, and hence binds to a specific antigen, the ERBB2 receptor.¹⁸ The ERBB2 protein, which binds the receptor, is overexpressed in some breast tumors.¹⁹ Like most effective small molecule drugs, antibodies bind only to specific epitopes (a part of a protein or other chemical signature that the antibody can recognize,) and an antibody to the ERBB2 receptor will be useful as a therapeutic agent only where blocking the ERBB2 protein from binding to its receptor will have some effect on the growth or progression of a tumor. Examining data following Phase III trials revealed that Herceptin was more effective in tumors where ERBB2 was overexpressed. Patients must take a diagnostic test to determine the extent of ERBB2 expression before they are prescribed Herceptin.

B. Pharmacogenomics

¹⁷ See *Roses*, *supra* note 1 at 648.

¹⁸ See *id.*

¹⁹ See *id.*

Pharmacogenomic technologies are primarily useful in two areas: gene expression analysis and examination of single nucleotide polymorphisms (SNPs) linked to phenotypes demonstrative of efficacy or safety. Other technologies, such as “metabolomics” or “proteomics” are similar in approach but utilize different analytes – metabolites and proteins, respectively. All of these technologies involve parallel monitoring of all analytes of a given type in a cell or tissue in response to different conditions, such as disease states.

Microarrays for Gene Expression

Microarray technology can be used to monitor the “transcriptome,” or the complete set of gene transcripts produced by a cell. Messenger RNA (mRNA) is an intermediate between genes and proteins. Ribosomes, complexes of RNA and protein, synthesize proteins from mRNA “transcripts” of DNA sequences. The mRNA sequences are essentially duplicates of the nucleotide sequences of genes. A cell does not need its entire complement of proteins produced simultaneously – in fact, this would be highly detrimental. Moreover, in complex organisms, all cells, even given highly divergent functions, contain complete copies of an organism’s genome. In order to respond to different conditions and develop different tissues to mediate diverse functions, regulation of gene expression at the cellular level is critical. Different genes will be expressed in different cell types and under different conditions. Gene regulation occurs at many stages, but the most energetically efficient regulation of gene expression will modulate the concentration of mRNA. Cells accomplish this modulation through control of the rates of mRNA synthesis from genes (transcription) as well as mRNA degradation and modification processes.

For example, suppose gene A encodes an enzyme involved in breaking down a given toxin. Under normal conditions, with scarce raw materials and energy, the cell will focus its productive capacities most efficiently elsewhere, producing structural proteins or proteins that mediate basic metabolic functions. When the cell is exposed to increased quantities of the toxin, however, the cell will need increased quantities of the protein. The cell might then produce more of the mRNA transcript encoding the protein, or alter the mRNA or proteins that bind to it in such a way that it is degraded at a lower rate or “translated” into protein more quickly. Whether the degradation of the mRNA slows or its synthesis increases, the net result upon exposure to the toxin will be an increased concentration of the mRNA transcript of gene A.

Microarrays allow a “snapshot” of all of the mRNAs in a given population of cells given a change in condition.²⁰ A microarray is typically a glass slide, about 1 cm² upon which whole genes or fragments of genes representing the entire known complement of genes of a given organism, or a set of genes known to be expressed in a given tissue, has been arrayed in “spots” in a regular fashion. The mRNA from a given sample – typically a time point²¹ – will be fluorescently labeled. These fluorescent copies will then be put in contact with the microarray surface and allowed to bind (“hybridize”) through specific base-pair interactions to the genes or gene fragments on the array. Depending on the array system, the relative concentrations of a given gene can be determined by level of fluorescence on two different arrays, or by relative amounts of samples in a given spot labeled to fluoresce with different colors on the same array.²²

The ability to follow all genes simultaneously is crucial. To return to the example of “gene A,” inevitably, the A enzyme will not act alone in response to the introduction of the toxin, but as part of a complex of

²⁰See, e.g., Mark Schena, et al., *Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray*, 270 SCIENCE 467 (1995)

²¹a sample taken at a fixed interval, as in any Phase I clinical trial

²²See Schena, *supra* note 20; Deval A. Lashkari, et al., *Yeast Microarrays for Genome Wide Parallel Genetic and Gene Expression Analysis*, 94 PROC. NAT’L ACAD. SCI. 13057 (1997)

proteins or simply as one component of a metabolic pathway. Changes in the concentrations of the mRNA encoding at least some of those proteins would be predicted as well.²³ Hence, microarrays are a useful tool for scientists seeking to understand how gene products act in concert, or how a cell deals with different stresses or conditions on the level of the entire genome. Furthermore, if the function of a gene product is unknown, its patterns of expression across a range of conditions might provide some clues.

Beyond these basic research applications, microarrays are useful in drug development and diagnosis through the establishment of biomarkers and identification of target genes. Essentially, the patterns of expression elucidated on an array in response to a certain condition may provide valuable information even where important components of a pathway are not regulated at the transcriptional level, or where the function of certain genes is unknown. For example, patterns of expression may be seen to repeat whenever compounds are toxic or carcinogenic in animals, or where a favorable treatment outcome, such as remission of a tumor or reduction of a toxic metabolite develops.²⁴ Where such patterns could be used to reliably predict treatment outcomes, the patterns could act as “biomarkers,” potentially rendering drug development more efficient by more accurately predicting long-term outcomes in shorter intervals.

In 2001, an NIH working group defined a “biomarker” as “a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention,” and put biomarkers in three classes: “those that track disease progression over time and correlate with known clinical measures; those that detect the effect of a drug; and those that serve as surrogate endpoints.”²⁵

²³There are, of course, ways a cell could deal with a change in conditions that might not be detectable as a change in mRNA concentration. For example, numerous protein-protein interactions are mediated by the phosphorylation of proteins or other post-translational modifications.

²⁴See Julie Wakefield, *FDA Eyes Pharmacogenomic Data*, 112 ENVTL HEALTH PERSPECTIVES A217 (2004).

²⁵Jennifer Van Brundt, *Biomarkers, The Pendulum Finally Swings*, SIGNALS MAGAZINE (October, 2004), at

Biomarkers that act as surrogate endpoints may be especially useful in clinical trials and treatment. For some conditions, it will not be feasible to direct a clinical trial that monitors patients for the duration necessary to observe the desired treatment outcome. If a biomarker can be established early in the course of treatment, the ultimate success of a drug can be established faster, and at much lower cost. The same is true for biomarkers indicative of toxicity. For example, carcinogenicity could be detected early in animal trials, enhancing safety.

SNPs

Researchers can also use parallel systems to type patients for single nucleotide polymorphisms, or “SNPs.”²⁶ SNPs are useful both for mapping genes, and as a readily detectable indicator of genotype, given close linkage to a gene or trait of interest. Mapping is a statistical technique based on the premise that adjacent areas of a chromosome will cosegregate more frequently than distal areas during meiosis, when recombination occurs between the copies of chromosomes inherited from each parent during the formation of germ line cells. If, to a first approximation, the frequency of chromosomal crossover at any given point along a chromosome is equal, the closer together two sequences are, the less frequently a crossover will occur between them, and the more frequently they will be observed on the same chromosome.

Linkage disequilibrium (LD) studies are useful for finding the genetic bases for complex traits – phenotypes governed by multiple genes. Essentially, if certain SNPs are seen to comigrate more frequently than would be expected from random mating in the population, it is likely that both loci are somehow involved with

<http://www.signalsmag.com/signalsmag.nsf/0/4D214C0B5216A2BC88256F3300693C21>

²⁶See Anne-Christine Syvanen, *Assessing genetic variation: genotyping single nucleotide polymorphisms*, 2 NATURE REVIEWS: GENETICS 930 (2001) (“Comparison of genomic DNA sequences in different individuals reveals some positions at which two, or in some cases, more than two, bases can occur. These single nucleotide polymorphisms (SNPs)... are estimated to occur at one out of every 1,000 bases in the human genome.”)

the maintenance of the phenotype of interest, such as positive response to a drug.²⁷

A number of methods exist allowing genotyping of SNPs, including those utilizing microarrays.²⁸ The Affymetrix “GeneChip” system, a microarray system also used in gene expression studies, allows sufficiently high density arraying of oligonucleotides (10^6 oligonucleotides per cm^2) to allow sequences containing a number of different possible SNPs (allele specific oligonucleotides, or “ASOs”), along with flanking sequences.²⁹ When a sample, generated by PCR amplification of a given region of a subject’s genomic DNA, is added to the array, more stable hybridization will generally occur where the printed oligonucleotides more closely complement the oligonucleotides in the sample.³⁰ Other techniques utilize various enzymes’ abilities to recognize and differentiate between double stranded DNA structures and double-stranded structures interrupted by a mismatched pair of nucleotides. Methods using PCR take advantage of two activities of DNA polymerases, both an exonuclease activity that degrades double stranded sequences, and the polymerase activity itself, which will be inactive if blocked by a mismatch.³¹

Among the greatest benefits of pharmacogenomics to the pharmaceutical industry could be the use of genetic biomarkers such as SNPs to enrich clinical trials for responsive patients.³² According to Glaxo researcher Allen Roses, “[i]n practice, most candidate drugs that reach human testing fail in Phase IIA.”³³ Pharmaceutical companies tend to abandon drugs in development if there is efficacy only in a small subgroup.³⁴ If pharmacogenetic tests could allow for differentiation between a small set of responders and a larger set

²⁷See Roses, *supra* note 1 at 648.

²⁸See Syvanen, *supra* note 26 at 933.

²⁹See *id.*

³⁰See *id.*

³¹See *id.*

³²See Roses, *supra* note 1 at 647.

³³*Id.* (“Phase IIA is the first time that a molecule is tested for its desired clinical effect in humans.”)

³⁴See *id.* at 648.

of non-responders, development could move forward, with trials enriched for individuals positive for that biomarker.³⁵

III. FDA GUIDANCE

In human trials, the correlation of expression biomarkers, for both safety and efficacy, and genetic biomarkers could work to select a specific group of patients for whom a given treatment is safe and effective. Such an application of pharmacogenomic technology would allow treatment very close to “individualized medicine.” Much like Herceptin, a medication could be marketed with a genetic test that will be used to determine whether the medication will be safe or effective for a given patient at a given dose.

Before entering the marketplace, however, pharmacogenomic techniques must be proven effective in predicting outcomes, and it is the FDA with whom the decision regarding the reliability of clinical trials has been entrusted. In order to facilitate this sort proof of principle on a large scale – and to a degree of proof that will allow the public confidence in the efforts of the biotech and pharmaceutical industries – the FDA has released its first guidance to solicit pharmacogenomic data submissions from pharmaceutical companies.

In November of 2003, the FDA published a draft guidance designed to introduce both the agency and pharmaceutical manufacturers to the use of pharmacogenomic data in submissions to be evaluated by the FDA.³⁶ The guidance subsumed the term “pharmacogenetics” under the broader term “pharmacogenomics” to define the field, but distinguished “pharmacogenetic tests,” defined as assays studying genetic variation “related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics)” from

³⁵See *id.*

³⁶See Guidance, *supra* note 3.

“pharmacogenomic tests,” which assay “variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response.”³⁷ Significantly, the guidance expressly disclaims any relevance to proteomic techniques, in which biotech companies are making large investments, and which the FDA will at some point need to explore.³⁸

The guidance does not require submission of pharmacogenomic data with all clinical trials. Submission is required only where pharmacogenomic data is obtained and relied upon for decision making during the IND or NDA phase. Under administrative law, none of the procedures are discussed in language that would suggest they are mandatory. The protocols discussed were not regulations promulgated through notice and comment rulemaking procedures. However, in practice, pharmaceutical companies will attempt to comply. Generally, however, the guidance does not make pharmacogenomic research a standard component of submissions because the FDA simply lacks the expertise with pharmacogenomic data to make regulatory decisions, and because “most experimental results may not be well enough established to be suitable for regulatory decision making.”³⁹ To assist in the standardization of procedures and to familiarize the FDA with pharmacogenomic data, the guidance introduces a format by which such exploratory data can be volunteered by drug companies.

Fundamentally, the guidance creates procedural distinctions based on the degree to which a given test has been proven reliable and empirically corroborated. The guidance defines a “valid biomarker” as a pharmacogenomic test which is “measured in an analytical test system with well-established performance characteristics” and for which “there is an established scientific framework or body of evidence that elucidates

³⁷*Id.* at 15.

³⁸*See* Van Brundt, *supra* note 25.

³⁹Guidance, *supra* note 3, at 2.

the physiologic, pharmacologic, toxicologic, or clinical significance of the test results.”⁴⁰ Essentially, any data presented to the FDA that was derived using a pharmacogenomic technique must be generated using a technique that is reliable and must have considerable empirical support. At this stage, then, it does not seem that a mere correlation between a pattern of gene expression and treatment outcome would be considered “valid” until some “elucidat[ion]” of the “scientific framework” within which the data can be understood. Some study of mechanism would appear to be necessary, especially for a result to have an empirical grounding similar to data regarding the cytochromes. The guidance offers the example of a genetic test to determine a patient’s CYP450 2D6 allele as a valid biomarker.⁴¹

The guidance further differentiates between “known” and “probable” valid biomarkers.⁴² “Known” valid biomarkers “have been accepted in the broad scientific community.” Data sufficient to validate a biomarker, but that have not been vetted by the scientific community, may establish a “probable valid biomarker.” Other pharmacogenomic data that may be useful in drug development need not be submitted.

Pharmacogenomic data is to be submitted as part of an IND under § 312.23 under three conditions: (1) the test results are “used for decision making”; (2) the test results are used to support scientific arguments; or (3) the results are a known, valid biomarker. At the NDA stage, pharmacogenomic data intended to be included in the label are to be submitted with the NDA. Data on known or probable valid biomarkers are to be submitted with the NDA as “abbreviated reports.”⁴³

The guidance recognizes that most pharmacogenomic data will not meet the requirements for known or

⁴⁰*Id.* at 4.

⁴¹*Id.*

⁴²*Id.*

⁴³*Id.* at 9.

probable valid biomarkers.⁴⁴ Because the FDA anticipates that pharmacogenomic data will be a standard component of future submissions, however, the guidance establishes a structure submission of exploratory pharmacogenomic data as “voluntary genomic data submissions” (VGDSs).⁴⁵ VGDSs will be reviewed by an “Interdisciplinary Pharmacogenomic Review Group” (IPRG).⁴⁶ The FDA contemplates that such submissions might include gene expression data obtained using microarrays or SNP profiling of participants in clinical trials.⁴⁷ The FDA is adamant that data submitted under the voluntary protocols will not affect the approval process. Only if further information indicates that the data in the VGDS must be submitted with an NDA or BLA will the data be required to be resubmitted and used in the approval process.⁴⁸

IV. ANALYSIS – THE GUIDANCE AND THE ROLE OF THE FDA

The issuance of the 2003 guidance was preceded by a meeting of a working group involving representatives from the FDA, the Pharmacogenetics Working Group (PWG), the Pharmaceutical Manufacturers of America (PhRMA), and PhRMA’s Preclinical Safety Committee (DruSafe) in May, 2002.⁴⁹ The workshop concluded that although pharmacogenomic technologies have potential to improve the safety and efficacy of

drugs when used at all stages of clinical trials, because the technologies are new and largely unproven, regulatory bodies and developers must establish certain standards and reference populations for pharmacogenomic analysis. For example, the workshop report notes that both sample size requirements and the ethnic composition of groups involved in pharmacogenomic studies must be established.⁵⁰ Given multiple methods of SNP

⁴⁴See *id.* at 6.

⁴⁵*Id.*

⁴⁶*Id.*

⁴⁷See *id.* at 10.

⁴⁸See *id.* at 11.

⁴⁹See Lesko, *supra* note 2.

⁵⁰See *id.* at 344.

detection, pharmaceutical manufacturers would have a strong interest in having FDA develop a standard for validation before investing in the infrastructure necessary to generate data using a given technique, as well. The workshop report notes that “[w]ith regard to the use of SNP and haplotype assay technology and the validation of these methods, there was consensus for a need for standardized reference materials, standards for assay validation, and specific regulatory guidance for validation criteria of the methods.”⁵¹

For microarray data, there was concern that methods were not yet sufficiently reproducible to be useful in a clinical setting. Generally, it was recognized that microarray data is highly cumulative, and that a large database would be beneficial. Many participants suggested that the FDA require any microarray data from experiments with compounds for which an IND has been filed.⁵² Because data could become more informative after submission but before approval, all participants wanted “highly transparent” FDA procedures.⁵³

With regard to the use of pharmacogenomic tests in clinical trials, the workshop found promise in all stages. The report notes that the administration of a range of doses during Phase I is especially useful in conjunction with pharmacogenomic and pharmacogenetic tests, offering an opportunity to correlate gene expression with dose and response, and to examine adverse events more fully.⁵⁴ There was some debate among workshop participants regarding whether adverse events correlated with genotype would warrant stratification or even require inclusion or exclusion at Phase II, with some participants suggesting that data that was exploratory at Phase I could be confirmed during Phase II given the broader samples utilized.⁵⁵ Well-established biomarkers, such as the CYP2C and D family, were felt to be sufficiently validated to allow

⁵¹*Id.*

⁵²*See id.* at 345.

⁵³*Id.*

⁵⁴*See id.* at 349.

⁵⁵*See id.*

them to act as

inclusion/exclusion or stratification criteria.⁵⁶ Generally, “there [was] more willingness to stratify based on pharmacogenomics and pharmacogenetics for safety than for efficacy.”⁵⁷ For well-studied genes such as the cytochromes, an analogy could be drawn “to the study of patients with reduced renal function,” and hence, developers would have some experience administering trial representation in this manner.⁵⁸

For broader, Phase III trials, the report notes some question regarding the breadth of the test pool given some indication from earlier phases that the safety or efficacy of a drug will vary with genotype.⁵⁹ Though a correlation might be seen between genotype and therapeutic outcome in early stages, testing on individuals negative for the biomarker indicative of favorable outcome might still be beneficial. This benefit would derive not only from the opportunity to examine further data to validate the biomarker at issue. Additionally, one might expect that, even given biomarkers indicative of safety or efficacy, the medications will be used by patients who are negative for the relevant biomarker.

Given this background, it is worth asking whether the FDA guidance of 2003 promulgated the best possible system for balancing economic incentives, consumer welfare, and a need to shepherd pharmacogenomic technology to maturity. Though the FDA recognizes “concern” among pharmaceutical manufacturers that it will have some difficulty incorporating pharmacogenomic data into the approval process, the guidance argues that the agency “has considerable experience” incorporating data that “predict increased risk of adverse events, or point to enhanced probability of response,” such as information on “drug metabolizing phenotypes”

⁵⁶ See *id.*

⁵⁷ *Id.*

⁵⁸ *Id.* at 350.

⁵⁹ See *id.* at 352.

or “conditions or co-factors that may increase an individual’s susceptibility to an adverse event.”⁶⁰ Among this latter category, the guidance lists “co-morbid conditions, metabolic susceptibilities such as renal or hepatic failure, or interacting drugs.”⁶¹ Generally, the FDA does not anticipate that pharmacogenomic data will “give definitive answers about safety and effectiveness in subpopulations.”⁶² Rather, pharmacogenomic data will be one factor among many influencing how patients respond to treatment, and hence “genetic markers can ordinarily be handled like other predictive markers in the clinical area.”⁶³ In oncology, however, the agency predicts that the data may have more immediate and definitive impact.⁶⁴

With respect to biomarkers indicative of toxicity, the gradual process anticipated by the FDA is probably an accurate prediction of how pharmacogenomic data will be introduced to the drug development process. A study conducted by the Wellcome Trust examined the clinical use of clozapine, an antipsychotic drug used among patients for whom other drugs are either ineffective or cannot be tolerated.⁶⁵ Clozapine can cause agranulocytosis, a potentially fatal blood disorder.⁶⁶ Clinicians were skeptical that a test could predict the occurrence of the disorder to an extent that would obviate expensive blood monitoring, and given the use of clozapine in patients who had not responded to other drugs, clinicians were reluctant to rule out patients based on genetic data.⁶⁷ There was also concern that treatment endpoints for schizophrenia were difficult to establish,

⁶⁰Guidance, *supra* note 3 at 13.

⁶¹*Id.*

⁶²*Id.* at 14.

⁶³*Id.*

⁶⁴*See id.*

⁶⁵Andrew Webster, et al., *Integrating Pharmacogenetics into Society: In Search of a Model*, 5 NATURE REVIEWS: GENETICS 663 (2004).

⁶⁶*See id.* at 665.

⁶⁷*See id.*

making biomarkers difficult to establish, as well.⁶⁸

Given the difficulties accompanying the introduction of pharmacogenomic information at the clinical level, the FDA's cautious approach is understandable. Unless a diagnostic test is developed rigorously alongside a medication, it is unlikely that genetic information will provide more than a loose correlation between genotype and treatment outcome – a correlation that may not justify denying a patient treatment, depending on the clinical context.

The FDA's refusal to require submission of or base approval on the sort of pharmacogenomic research considered appropriate for VGDS submission is also likely an appropriate protocol to foster development of pharmacogenomics without overly hindering research by requiring use of an unproven technology. For pharmacogenomic techniques such as microarrays and SNP mapping to become commonplace, more data are needed. The more conditions under which gene expression is studied, the more robust and reliable certain biomarkers will be. For example, the same set of genes may be seen to exhibit changes in expression in response to a certain class of medicines, but only given one of two genotypes for cytochromes or transport proteins. While the FDA can play a role in encouraging pharmaceutical companies to use pharmacogenomic testing or pool results, ultimately, the sort of basic research infrastructures necessary to improve the reliability of pharmacogenomic data will likely need to come from other sources.

⁶⁸*See id.*

For example, as new SNPs have been discovered in the human genome, they have been placed in the public domain by a consortium of pharmaceutical companies and research institutions with the understanding that they will ultimately be of greater benefit as a publicly available resource.⁶⁹ Similar efforts to create a database of microarray data would also be highly beneficial. For these data to be useful, however, some greater standardization of protocol is likely needed, so that meaningful comparison of data can be undertaken. The FDA could be instrumental in developing such standards through analysis of its analysis of VGDS data.

In developing a protocol for submission of pharmacogenomic and other data, FDA must accommodate both the rapid development of array technology and the evolution of similar technologies such as proteomics and metabolomics. Both of these issues present the same basic challenge – ensuring that FDA procedures are able to accommodate technological growth without requiring a disruptive paradigm shift in clinical testing protocols or submission format.

Ideally, data in each area – gene expression, proteomics or metabolomics – would be sufficiently standardized to allow comparisons across the widest possible range of conditions. Additionally, any standard must be independent of any individual platform, to avoid unduly hindering advances in the underlying technology.

(1) *Technique validation*

The FDA could move to sanction platforms through a formal review process in much the same way that diagnostic tests are validated. Because platform approval would consist of a “proof of principle” pilot

⁶⁹See Barbara Ann Binzak, *How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the Drug Approval Process*, 58 FOOD & DRUG L. J. 103 (2003)

experiment designed to replicate the data of a previous clinical trial, the FDA would likely have the expertise to evaluate platforms thoroughly and fairly. Initially, proof of principle studies would be performed on existing drugs or known conditions, such as ERBB2 overexpression in some breast tumors.

(2) Ongoing controls

Once a technique is shown reliable and approved, data may be submitted, initially as part of a VGDS, and eventually with all INDs or NDAs. Eventual mandatory submission is desirable to increase the total pool of publicly available data for the synergistic benefits described above. Each submission should include proper controls to both demonstrate proper experimental design and to verify the efficacy of the technique. To the extent possible, conditions should be standardized to facilitate comparison. For example, tissue quantities tested could be correlated to *in vivo* concentration of a given drug. Control samples should be verified against the platform validation data to ensure reproducible results. Obviously, conditions and patient information must be rigorously detailed to allow sorting of data according to a number of fields (e.g., patient age, patient weight, renal function, other medications, and any genetic biomarkers assayed.)

CONCLUSION

Pharmacogenomics is not yet mature enough as a technology for FDA to mandate its submission with INDs or NDAs, with the possible exception of well-characterized metabolic enzymes explored using pharmacogenetic techniques. Providing companies incentive to submit data to a central database is a central challenge facing efforts to marshal the technology to maturity and common use. By setting standards for data submission that are relatively platform or technique independent, the FDA would allow the technology to continue to

develop, while at the same time facilitating cumulative data mining for greater understanding of underlying biological processes and adverse events. Until the platform technologies are validated, however, the FDA's largely voluntary submission system is advisable to create a dialogue between industry in the FDA whereby various obstacles such as standardization and sufficiency of validation of results can be discussed.